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10/799,238	03/12/2004	Elliott Richelson	07039-126002	7520

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EXAMINER	
EPPS SMITH, JANET L	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/799,238	RICHELSON ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Smith	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 15-26 are presently pending for examination.

3. Applicant's filing of an Appeal Brief on 12/10/2008 is noted, Appellant's arguments with respect to the enablement rejection of claims 15-26 are addressed below.

4. The instant application claims priority back to 10/17/1997.

Response to Amendment

5. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Claim Rejections - 35 USC § 112

6. The rejection of claims 15-26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in response to Applicant's amendment to the claims.

7. Claims 15-26 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the NTRA-PNA oligomer to "engender a biological response" in a rat challenged with neurotensin, and for reducing the expression of a target nucleic acid comprising the delivery of a polyamide nucleic acid oligomer comprising a neutral amide backbone, and comprising a sequence complementary to said target nucleic acid, does not reasonably provide enablement for the amelioration of any and all disease conditions in any mammal comprising the

delivery of ***a molecule comprising a polyamide nucleic acid oligomer***, and having a sequence complementary to a target nucleic acid, wherein the overexpression of said target nucleic acid is associated with said disease condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

8. Applicant's arguments filed 12/10/2008 have been fully considered but they are not persuasive.

9. Applicants traversed the instant rejection on the grounds that:

"[W]e do not agree with the Examiner's characterization of the claims vis-/~-vis enablement. Claim 15 recites administering to the cells a polyamide nucleic acid oligomer under conditions wherein the polyamide nucleic acid oligomer engenders a biological response in a sequence specific manner. A "biological response" would be understood by persons of skill in the art to include reducing the expression of a target nucleic acid. See, e.g., page 15, lines 3-16 of Applicants' specification.

There is no language in claim 15, or in any of the dependent claims, that states that the engendered biological response must be effective to treat "any disease associated with a target nucleic acid," as the Examiner appears to contend. Thus, any biological response engendered via the polyamide nucleic acid oligomer that is in a sequence specific manner would meet the claimed limitation of a "biological response," including reducing the expression of a target nucleic acid. While Applicants' specification discloses using polyamide nucleic acid oligomers treat diseases...the presently pending claims are not limited to this use."

10. Contrary to Applicant's assertions, the instant claims recite a "method of treating cells present in a mammal..," wherein said method comprising administering to said cells *in vivo*. Although the claims do not recite wherein the claimed method reads on a "method of treating" a disease in an animal, the instant claims do not recite any description regarding what the cells in the mammal are being "treated" for. Due to the breadth of the instant claims, and in light of the description of the methods encompassed by the claimed invention in the specification as filed, it is clear that the scope of the instant claims encompass methods of treating a disease since this is

clearly set forth in the specification as filed, see e.g. bridging ¶ of pages 4-5, which recites:

11. "[I]n addition, this invention provides for the **treatment of cells in vivo such that a behavioral response is observed in an organism**. Thus, this invention describes methods and materials that allow any polypeptide to be manipulated and studied in living cells. For example, the expression of a specific polypeptide can be knocked-out in adult organisms for the duration of PNA oligomer treatment. In addition to greatly aiding the advancement of basic scientific research, this ability to manipulate polypeptide **expression and thus function in a sequence specific manner is clearly beneficial to gene therapy approaches involving the treatment of cancer, aging, behavioral diseases, infections, and auto-immune diseases**."

12. Furthermore, Applicants argued that the Examiner appears to acknowledge, it is clear from the record of the present application, and the records of multiple related application records that "no undue experimentation is needed to administer a polyamide nucleic acid as recited in the pending claims to engender a biological response ins a sequence specific manner." Applicants also provided multiple copies of declarations filed during the prosecution of US Patent Application Nos. 09/168,791, 08/953,269, and 09/016,685. Thus, Applicants argued that the specification fully enables the presently pending claims.

13. The examiner agrees that the multiple Declarations filed under 37 CFR § 1.132 demonstrate the *in vivo* administration of multiple specific PNA oligomers targeting a variety of mRNA targets, wherein a sequence specific biological response was detected after *in vivo* administration of the PNA oligomer. However, to the extent that the instant claims have been amended to recite the administration of polyamide nucleic acid oligomers, "[w]herein said polyamide nucleic acid oligomers contain ***a sequence*** complementary to a target nucleic acid present in said mammal," the experimental data

set forth in the Declarations filed in the related applications are not commensurate in scope with the claims of the instant claims. The scope of the instant claims can be interpreted as encompassing polyamide nucleic acid oligomers comprising a sequence that is not fully complementary to the target nucleic acid, i.e. comprising a partial complementary sequence to the target, or comprising an undefined number of mismatches.

14. According to Nielsen et al. (1993) PNA do not bind to its target nucleic acid when the PNA contains more than one mismatch to its target sequence. Therefore, to the extent that the claimed methods, which comprise administration of PNA oligomers that contain ***a sequence*** complementary to the target nucleic acid, i.e. wherein an undefined number of mismatches are encompassed by the PNA oligomer, Applicant have not provided sufficient guidance for practicing the full scope of the claimed invention.

15. Moreover, Applicant's own specification provide a list of problems known to be associated with the use of polyamide nucleic acid oligomers at the time of filing of the instant application, see for example the following passage taken from page 2 of the specification as filed:

"Recent strategies devised to improve cellular uptake of PNA oligomers involve conjugating other molecules to PNA sequences. Specifically, conjugating a small peptide sequence that binds the insulin-like growth factor 1 receptor (IGF1R) to a PNA oligomer increases cellular uptake of labeled PNA sequences by IGF1R-expressing cells, whereas conditions using unconjugated PNA sequences or cells lacking IGF1R show ***negligible cellular uptake*** (Basu S. and Wickstrom E., *Bioconjugate Chem.* 8:481-488 (1997)). These results suggest that conjugating receptor ligand molecules to PNA oligomers can increase cellular uptake; *however, the ability of these receptor ligand-conjugated PNA oligomers to influence biological activity once inside the target cells remains unknown.* Further, PNA oligomers will gain entrance only into cells expressing that particular targeted receptor. ***Thus, an appropriate ligand molecule would have to be designed and coupled to PNA oligomers for each cell type of interest. In addition, the level of receptor expression can influence the permeability of ligand-conjugated PNA oligomers.***"

The instant claims broadly read on the administration of a polyamide nucleic acid oligomer of undefined structure and modification, and further comprising an undefined degree of complementarity to the target nucleic acid. However, Applicant's own specification states that in order for PNA oligomers to gain entrance into cells, an appropriate ligand molecule would have to be designed and coupled to the PNA oligomer for each cell type of interest. Applicants have not provided sufficient guidance and/or instruction that would have allowed the skilled artisan following the teachings in the specification as filed to practice the full scope of the claimed invention without further undue, and unpredictable experimentation to design the appropriate ligand molecule to conjugate to the PNA oligomers in order to achieve cellular uptake into each cell type of interest, and furthermore achieve a sufficient concentration of PNA oligomer into each cell type of interest in order to produce the desired biological response.

Applicants do not clearly define how the polyamide nucleic acid oligomers of the instant claims structurally differ from the prior art PNA oligomers that are known in the art to have negligible cellular uptake and require conjugation to a ligand specific for a particular cells type in order to achieve cellular uptake and produce a biological response. Other than the use of the specific PNA oligomers according to the present invention, Applicants have not provided clear evidence that their disclosed experimental results using the particular PNA oligomers described in the specification as filed, can be achieved using any generic polyamide nucleic acid oligomer as recited in the instant claims. According to the specification as filed the polyamide nucleic acid oligomers of

the claimed invention were synthesized with Fmoc-N-(2-aminoethyl)glycyl PNA oligomers, see Example 1, page 27. However, the instant claims generically recite the administration of polyamide nucleic acid oligomers comprising a neutral amide backbone. Therefore other than the use of polyamide nucleic acid oligomers synthesized according to the present invention, particularly those synthesized using Fmoc-N-(2-aminoethyl)glycyl monomers, and having a sequence that contains no more than a single mismatch with its target nucleic acid, Applicants have not provided sufficient guidance that would allow the skilled artisan to practice the full scope of the claimed invention without undue experimentation.

As stated in the prior Office Action, according to Rasmussen et al. (2006; see page 44, 2nd paragraph): "[T]o date, the published studies of PNA in cellular systems often represent isolated efforts in which a certain delivery protocol has been used in a single cell type during the investigation of a given gene by a specific methodology. The diversity in cell type, application, and methodology in these papers makes it virtually impossible to make reliable assessments about the relative efficiency of the different protocols." Moreover, Rasmussen et al. compared the efficacy of different transfection protocols. The study concluded with the following paragraph (see page 56):

"A final and important lesson from the present study was the finding that because of uncontrollable biologic factors, the absolute optimal transfection conditions will vary from experiment to experiment. Thus, to achieve really optimal cellular delivery of PNA in a specific experiment, these variations should be taken into account. This means that even though an optimized transfection protocol has been established, each experiment should include a systematic variation (around the optimal values) of critical transfection parameters, such as the concentration of PNA or the transfection reagent."

It is noted that the instant specification was filed on 3/12/04, however it claims priority back to 10/17/1997. As per MPEP § 2164.05(a) [R-2] "[W]hether the

specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art. The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b). The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

In the instant case, the Declaration evidence provided by Applicants do not address the unpredictability associated with significantly low cellular permeability known to be associated with PNA oligomers such that the skilled artisan following the teachings of the specification as filed would have been able to overcome this well known obstacle associated with the use of PNA oligomers *in vivo*. As stated in the prior Office Action, based upon the disclosures of Tyler et al. (1998), Koppelhus et al. (2002) and Rasmussen et al. (2006), it is clear that even today there is a significant level of unpredictability associated with the *in vivo* efficacy of PNA oligomers, particularly in regards to the variation in behavior of the oligomer as it relates to different cell types

and methodology. Therefore, since the state of the art in regards to the use of PNA oligomers in antisense or antigene therapy remains unpredictable (as evidenced by the above references) it is concluded that the skilled artisan would have had to resort to undue experimentation to practice the full scope of the claimed invention due to significant breadth of the claims, the known unpredictability associated with the cellular uptake of PNA oligomers into cells, and the known variability associated with PNA behavior in different cells types, and the limited guidance provided in the specification as filed.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

17. Claims 15-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Buchardt et al. (US 2002/0146718).

18. The prior art is applied to the extent that Applicants argue that the instant claims do not read on a method of treating a disease in a mammal, but encompass merely administering a PNA oligomer to cells in a mammal produce a biological effect, which includes reduction of expression of a polypeptide.

19. The PNA oligomers of Buchardt et al. are a novel class of compounds, known as peptide nucleic acids, which bind complementary DNA and RNA strands more strongly than a corresponding DNA strand, and exhibit increased sequence specificity and binding affinity, see Abstract.

20. Buchardt et al. the a method of administering PNA oligomers to the cells in a mammal, see the following ¶s:

> [0087] In general, for therapeutic or prophylactic treatment, a patient suspected of requiring such therapy is administered a compound of the present invention, commonly in a pharmaceutically acceptable carrier, in amounts and for periods of time which will vary depending upon the nature of the particular disease, it's severity and the patient's overall condition. The peptide nucleic acids of this invention can be formulated in a pharmaceutical composition, which may include carriers, thickeners, diluents, buffers, preservatives, surface active agents and the like. Pharmaceutical compositions may also include one or more active ingredients such as antimicrobial agents, anti-inflammatory agents, anesthetics and the like, in addition to the peptide nucleic acids.
>
> [0088] The pharmaceutical composition may be administered in a number of ways depending upon whether local or systemic treatment is desired, and upon the area to be treated. Administration may be topical (including ophthalmic, vaginal, rectal, intranasal, transdermal), oral or parenteral, for example, by intravenous drip, subcutaneous, intraperitoneal or intramuscular injection or intrathecal or intraventricular administration.

21. Since Buchardt et al. teach the general method of administering PNA oligomers in a mammal, wherein said PNA oligomer is complementary to a target nucleic acid, absent evidence to the contrary, the PNA oligomers of Buchardt et al. would possess the same characteristics as those set forth in the methods of the instant claims.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633